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July 5, 2000

Bonnie M. Lee
Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Dear Ms. Lee:

re: **Document No. OOD - 0805**
Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors: Exception from Informed Consent Requirements for Emergency Research

The **Applied Research Ethics National Association** (ARENA) and **Public Responsibility in Medicine and Research** (PRIM&R) wish to comment on the FDA's draft Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors: Exception from Informed Consent Requirements for Emergency Research. We found the draft commendable and helpful in general. We will comment only on changes we recommend.

Public Responsibility in Medicine and Research (PRIM&R), a national nonprofit organization founded in 1974, is a strong advocate for ethical human and animal research. By holding between two and five annual, nationwide conferences and publishing reports, PRIM&R is committed to the advancement of strong research programs and the consistent application of ethical precepts in both medicine and research. The conferences, hosted in Boston and other U.S. cities, provide an educational forum for the analysis of various biomedical and bioethical issues.

ARENA, an affiliated organization of PRIM&R, was formally organized in 1986 to promote educational activities, networking, the resolution and/or amelioration of mutual problems, and the professional advancement of its members. ARENA is the only membership organization for those involved in the day-to-day application of ethical principles and regulations regarding research and clinical practice. Members of ARENA include administrators and members of IRBs or IACUCs, hospital ethics committees, patient advocacy groups, and researchers and other professionals interested in bioethics. ARENA holds two educational meetings annually, one for IRB issues and the other for IACUC issues, in conjunction with PRIM&R-sponsored conferences.

OOD-0805

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II. Study Design; Designs

This paragraph was confusing to some readers, especially when read in conjunction with the subsection Prospect of Direct Benefit in the same section. For instance, it might help to clarify if "prospect of direct benefit" includes receiving no more than 'standard care.' It is not clear what is meant by 'not receiv[ing] the standard treatment'; that phrase should be clarified.

There are more permutations of design than the two described in this section ('standard care plus intervention vs. standard care plus placebo'; and 'standard care vs. not receiving standard care'). Other permutations include the following.

- The intervention contradicts an element within standard care, and thus that element is dropped in the intervention arm; the design would be 'standard care-minus-contradictory-element plus intervention vs. standard care-including-that-element plus placebo.'
- Two or more different or competing standard treatments are compared; the design would be 'standard-1 care vs. standard-2 care.'
- The efficacy of a major element in standard care is itself being questioned; the design might be 'standard car-minus-questioned-element [perhaps -plus-placebo] vs. standard care-including-questioned-element.'

We note that the third permutation is likely to be difficult for many lay people to understand, and may be more difficult to justify bioethically. The FDA might consider adding a statement that the justification given for such a trial must be strong, and must be understandable by lay people.

V. Licensed physician concurrence required for IRB approval of the research

The draft wording should be clarified. The intent is that a licensed physician participate in the meeting[s] in which the IRB discusses the protocol (for both initial approval and continuing review), and that, if the IRB votes to approve or to continue the research, the licensed physician vote to approve or to continue (if s/he is an IRB member) or concurs (if a IRB consultant). The paragraph should mention participation in the meetings by the licensed physician.

VI. Community Consultation and Public Disclosure

The draft helps clarify both 'community consultation' and 'public disclosure.' We have observed that many clinical investigators and even some IRBs think that both are one and the same. We suggest adding to the introduction (p. 6) a brief paragraph that compares the two procedures, providing concrete example[s] if appropriate. The wording could be similar to: "'Community consultation' differs from 'public disclosure' because the former includes discussion[s] with and by a wide group of community people and representatives, and thus includes listening to them. 'Public disclosure,' on the other hand, is a process of informing (i.e., a one-way transfer of information) that need not include discussion and listening."

We are concerned how this section appears to define the **role and responsibility of the IRB.** The draft proposes major changes in that role and responsibility.

Currently the IRB's role and responsibility are to review, request appropriate modifications in, and approve or disapprove the research protocol [i.e., the plans for the research]. The IRB itself neither develops the research protocol, nor conducts or implements the protocol. The clinical investigator, and ultimately the sponsor, are responsible for developing all elements of the protocol, and for conducting and implementing the protocol that has been approved by the IRB. The IRB reviews all elements of the protocol: advertisements, recruitment scripts, consent document, the process of informed consent, the plans for the interaction of the clinical investigator with each participant volunteer from consent through the entire intervention, etc.

This draft, however, proposes that the IRB itself implement and conduct almost the entire protocol element of community consultation. We believe the current model is in general sufficient and appropriate for most components of community consultation in Emergency Research, except for one significant component to be discussed below. In general, in most places in Section VI. where the draft states that the "IRB" should conduct, implement, or is responsible for an activity (other than review and approval), the draft instead should substitute "clinical investigator" or "sponsor and clinical investigator."

The exception, in which we agree that IRBs should have a more active role and responsibility, is an important component of community consultation: the IRB should directly listen to the community discussions and concerns expressed in those discussions, and not just listen through summary documentation by the clinical investigator. Three reasons support this more active role of the IRB.

- First, community consultation is new for everyone--sponsor, clinical investigator, and IRB alike.
- Second, the IRB is responsible for listening to and considering the community's opinions and concerns and feedback.
- Third, the IRB should assess and possibly incorporate those concerns and feedback into its decision-making about the protocol.

For those reasons, the IRB should neither rely on summaries nor have the concerns and feedback 'filtered' by others when it assesses the adequacy of the process, and when it uses the results of community consultation and discussion for its own decisions.

We believe that the draft should emphasize that the sponsor and clinical investigator have the primary responsibility to plan and conduct the process of community consultation, hearing the concerns and feedback, and making appropriate changes in the plans for the research (such as "excluding particular populations who voice opposition ..."). The draft should also give the reasons for the exceptional involvement of the IRB itself in this element of the research process. The draft should note that the IRB's expanded activity is to assure that the entire process is adequate. (Indeed, in many places the IRB actually has led the process of community consultation.) The draft then should state that the IRB:

- must review, request appropriate modifications in, and approve or disapprove the plans for community consultation;
- must have one or more members or senior IRB staff attend community meetings both to obtain feedback and hear concerns, and also to explain (if necessary) the proposed exception to informed consent;
- "might invite community representatives to participate in convened or special meetings of the IRB ...";

- must incorporate the concerns and feedback into its review, modifications requested, and approval of the protocol (that the sponsor and clinical investigator possibly had already changed based on community concerns and feedback they had heard).

We have three additional points. We strongly agree with the draft that "encourages sponsors to work with clinical investigators and IRBs in developing model strategies ...." The first sentence of the last paragraph of page 9 is ambiguous; better wording might be (with underline to show the difference from the draft), "The IRB must include in its minutes a written summary of the IRB's discussion of controversial issues and the IRB's resolution." A minor editorial point is that "medic alert" is a registered or copyrighted term (see http://www.medicalert.org).

VII. Contact of legally authorized representatives ....

On page 14, under Summary of contact efforts, the last sentence is ambiguous; better wording might be, "This summary must be provided to the IRB ...."

Throughout the draft

Where the draft states that "IRBs must find and document ...," better wording would be "IRBs must review, request appropriate modifications in, and approve [documentation of] [plans for] ...." We give two of several changes needed.

- In the subsection Public Disclosure, p. 10, the IRB should be "responsible for reviewing, requesting appropriate modifications in, and approving the process and content of public disclosure about the emergency research" (similar to what the IRB now does for recruiting advertisements).
- Under the section **Data Monitoring Committee (DMC)**, p. 15, "the IRB must review, request appropriate modifications in, and approve the sponsor's plans for and establishment of an independent DMC ...."

ARENA and PRIM&R strongly support the need for and usefulness of this Guidance. We congratulate the FDA on its efforts to develop a workable guidance to clinical investigators, sponsors, and IRBs for emergency research in which consent is waived. Thank you for giving us the opportunity to comment on this important proposed document.

Sincerely yours,

Sanford Chodosh, M.D.
President, PRIM&R and ARENA

Ada Sue Selwitz, M.A.
Co-Chair, ARENA Public Policy Committee

cc: ARENA Public Policy Committee

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